REMARKS

Claims 11 and 17-20 are pending. Claims 14-16 and 21-25 are withdrawn from consideration.

I. The Claimed Invention Is Novel

A. The Imura Reference

Claims 11 and 17-20 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent Application Publication 2003-0187038 (hereinafter, the "Imura reference"). Applicants traverse the rejection and respectfully request reconsideration thereof in view of the Rule 132 Declaration previously submitted.

The Office continues to assert that the Imura reference teaches that candesartan cilexetil can be used as a therapeutic agent for fibrinogen-related diseases of mammals, such as metabolic disorders, including Syndrome X (see, Final Rejection at page 10). Applicants have previously submitted a Declaration under 37 CFR § 1.132 in which Anders Ljunggren, a co-inventor of the present application, states that he is unaware of any causative link between fibrinogen levels in a human and syndrome X or metabolic syndrome in a human (see, paragraph 8) and that the Imura reference fails to provide any data (see, paragraph 6) or citation (see, paragraph 7) to support the position that syndrome X is a fibrinogen-related disease. Thus, the **bare** and **unsupported** statement in the Imura reference **CANNOT** be relied upon by one skilled in the art or the Office. Does the Office really consider that a single statement that a compound can be used to treat hundreds of diseases or disorders can be taken as enabling one skilled in the art to actually treat the hundreds of disorders?...particularly when the statement is not supported by any examples or any data? Does the Office really want to take the position that the Imura reference teaches one skilled in the art to treat myocardial infarction, stroke, nephritis, bedsore, lower limb gangrene, memory disorder, hepatitis, septicemia, eye diseases, inflammatory diseases, tumor, and toxemia with a single compound, in the absence of any examples or any data, without being required to perform undue experimentation? Applicants' Declaration under 37 CFR § 1.132 has not been refuted with any teaching set forth in the Imura reference. Accordingly, one skilled in the art would not rely upon the Imura reference as purported in the Final Rejection. Provided with these

facts, a person skilled in the art would not draw any conclusions as to the usefulness of angiotensin II inhibitors for treating metabolic syndrome.

Therefore, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn. If the Office maintains the present rejection, Applicants respectfully request that the Examiner discuss this rejection with the SPE.

B. The Terashita Reference

Claims 11 and 17-20 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent Application Publication 2006-0069133 (hereinafter, the "Terashita reference"). Applicants traverse the rejection and respectfully request reconsideration thereof because the Terashita reference is not proper prior art under 35 U.S.C. §102(e).

The relevant prior art date for the Terashita reference is its publication date of March 30, 2006, which is much too late. The PCT application from which the Terashita reference claims priority was not published in English. Thus, there is no 35 U.S.C. §102(e) date for the Terashita reference. See MPEP 606.02(f)(1). Even if the underlying PCT application was published in English and designated the United States, its priority date under 35 U.S.C. §102(e) could not be the filing date (i.e., 12/2002) set forth in the Final Rejection because foreign priority claims are not taken into consideration. See MPEP 606.02(f)(1). Thus, the Terashita reference is not prior art.

II. The Claimed Invention Is Not Obvious

Claims 11 and 17-20 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of: 1) U.S. Patent Application Publication 2003-0187038 (hereinafter, the "Imura reference"); 2) Yoneyama et al., Jpn. J. Pharmacol., 2002, 89, 193-196 (hereinafter, the "Yoneyama reference"); 3) World Health Organization document (hereinafter, the "WHO reference"); and 4) Ortlepp et al., Eur. J. Pharmacol., 2002, 436, 145-150 (hereinafter, the "Ortlepp reference"). Applicants traverse the rejection and respectfully request reconsideration because the combination of cited references fails to produce the claimed invention.

The combination of the cited references fails to produce Applicants' claimed methods. Applicants submit that their reasons of record remain applicable. In addition, the Office's use of the Imura reference is deficient. The Office asserts that the Imura reference teaches that candesartan cilexetil is useful as prophylactic or therapeutic agents for fibrinogen-related diseases of mammals, which includes metabolic disorders, such as Syndrome X . The Declaration under 37 CFR § 1.132 in which Anders Ljunggren, a co-inventor of the present application, states that he is unaware of any causative link between fibrinogen levels in a human and syndrome X or metabolic syndrome in a human (see, paragraph 8) and that the Imura reference fails to provide any data (see, paragraph 6) or citation (see, paragraph 7) to support the position that syndrome X is a fibrinogen-related disease is already of record. Thus, the bare and unsupported statement in the Imura reference cannot be relied upon by one skilled in the art. Accordingly, one skilled in the art would not rely upon the Imura reference as purported in the Final Rejection. The other cited references fail to cure this deficiency. Provided with these facts, a person skilled in the art would not draw any conclusions as to the usefulness of angiotensin II inhibitors for treating metabolic syndrome. Therefore, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

The Office asserts that the declaration is not persuasive because it only addresses 2 of the 8 Wands factors. There is no requirement that a Declaration under 37 CFR § 1.132 needs to address each Wands factor in order to be sufficient. Indeed, as the Office is well aware, opinion evidence relating to a fact issue should be considered by an Examiner. *In re Alton*, 37 USPQ.2d 1578, 1583 n.10 (Fed. Cir. 1996). Thus, the prior submitted Declaration in which one skilled in the art states that he is unaware of any causative link between fibrinogen levels in a human and syndrome X or metabolic syndrome in a human and that the Imura reference fails to provide any data or citation to support the position that syndrome X is a fibrinogen-related disease should be considered by the Office. The Office has not provided sufficient rebuttal evidence.

The Office asserts that the Example 1 of the Imura reference provides data demonstrating the reduction of fibrinogen levels. The Office also admits that "there is no data demonstrating efficacy in metabolic syndrome with humans or animal models" (see, Final rejection at page 3). Thus, what is missing from the Imura reference is data indicating that any of

the compounds recited in Applicants' claim 1 can be used to treat metabolic syndrome in a human. Thus, the Imura reference is deficient and not enabling. Thus, the other cited references I the rejection must cure the deficiencies of the Imura reference.

The Office asserts that a search of PubMed for "fibrinogen" and "metabolic syndrome" resulted in over 300 "hits" "indicating that there is much that is known in the art with respect to fibrinogen together with metabolic syndrome" (see, Final Rejection at page 4). The number of references, however, is irrelevant to an obviousness determination. The Office's attention on the Aso reference (i.e., Aso, Frontiers in Bioscience, 2007, 12, 2957-2966) is misplaced – its publication date is 2007, which is much too late. Thus, the Aso reference is irrelevant for prior art purposes. Citation of any other reference is also irrelevant for purposes of the present rejection since such references are not included within the rejection itself.

The Office's referral to the Cooke reference (i.e., Cooke et al., Blood Coagul Fibrinolysis, 2000, Abstract) is also misplaced. In contrast to the assertions and conclusions set forth in the Final Rejection, the Cooke references states that the "comparable age-adjusted odds ratio for hyperfibrinogenaemia was **non-significantly** higher" in subjects with metabolic syndrome when compared with those with no metabolic abnormalities. Thus, the link the Office tries to establish between fibrinogen and plasma viscosity is NOT made in the Cooke abstract.

The Office also states that because the Background section of the Imura references states that AII antagonistic activity are known to be therapeutic agents for hypertension, and hypertension is one feature of metabolic syndrome, then one skilled in the art would consider it to be obvious to treat metabolic syndrome with an AII antagonist. The Imura reference, however, does not teach or suggest that simply treating hypertension would have any effect, let alone a therapeutic effect, in treating the underlying metabolic syndrome. For example, treating a person having the common cold with cough medicine may alleviate a symptom of the cold (i.e., coughing), but does nothing to treat the underlying viral infection.

The Office also asserts that motivation is provided by the Ortlepp reference for replacing irbesartan with one of the compounds recited in Applicants' claim 1. As a preliminary matter, the Ortlepp reference reports a study comparing the effect of an ACE inhibitor and the effect of an angiotensin II inhibitor on hypertension, cardiac hypertrophy, hyperinsulinemia and atherosclerotic plaque in mice. In contrast, the present invention is directed to treating metabolic

syndrome in a human by administering one or more of several recited angiotensin II type 1 receptor antagonists. The Ortlepp reference is, thus, irrelevant for the present invention, which regards humans.

As pointed out in Applicants' specification, metabolic syndrome is a definition made by the World Health Organization (WHO) and refers only to human beings (see, page 2, lines 7-20 of the published PCT application). The section reads:

> *The metabolic syndrome*
> The metabolic syndrome is herein defined in accordance with the definition of the World Health Organization, i.e. according to the following criteria [World Health Organization (WHO). Department of Noncommunicable Disease Surveillance. Geneva: WHO 1999 pp 1-59]:
>
> 1. Fasting plasma glucose above 6.1 mmol/L
>
> 2. Blood pressure above 140/90 mm Hg
>
> 3. One or more of the following:
>
> a) Plasma triglycerides above 1.7 mmol/L and/or HDL below 0.9 mmol/L (men), below 1.0 mmol/L (women)
>
> b) Body mass index above 30 kg/m2

All these parameters refer to humans. It is, therefore, incorrect to state that the mice in the Ortlepp reference suffered from metabolic syndrome. For example, one of the parameters for being diagnosed as having metabolic syndrome is having a body mass index above 30. To calculate body mass index, the weight of the patient, in kilograms, is divided with the length of the patient multiplied by itself, measured in meters. Obviously, body mass index in the WHO definition of the metabolic syndrome, does not apply to mice.

Further, there is no baseline given in the Ortlepp reference for plasma triglycerides. For placebo, it is given at a level lower than the definition of a human diagnosed with metabolic syndrome would have. There is no teaching or suggestion in the Ortlepp reference of what the threshold would have been, would there have been a definition for metabolic syndrome in mice.

Yet another parameter for diagnosing a human as having metabolic syndrome is a blood pressure over 140/90 mmHg. The baseline for the mice in the study disclosed in the Ortlepp reference is about 110/73.

The mice participating in the study reported in the Ortlepp reference would not have fulfilled the parameters to be diagnosed with having the metabolic syndrome, had they been humans. Indeed, the mice of the Ortlepp reference did not have metabolic syndrome according to the WHO definition. They did not even have high blood pressure according to the definition. Thus, the Ortlepp reference does not disclose the treatment of the metabolic syndrome as defined in the specification, i.e. humans fulfilling the WHO parameters above. Given these facts, a person skilled in the art would not draw any conclusions as to the usefulness of angiotensin II inhibitors for treating metabolic syndrome.

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Office is invited to contact Applicants' undersigned representative at 610.640.7859 if there are any questions regarding Applicants' claimed invention.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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Date: **4 October 2010**

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